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VALVULAR HEART DISEASE

RECOMBINANT APOLIPOPROTEIN A-I MILANO DECREASES LEAFLET INFLAMMATION AND CALCIFICATION IN EXPERIMENTAL MODELS OF AORTIC STENOSIS

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Background: Aortic stenosis (AVS) is associated with significant morbidity and mortality. ApoA-I Milano (ApoA-IM), a mutant form of ApoA-I, rapidly regresses established atherosclerotic lesions and associated inflammation. Recent data suggest that ApoA-IM may also reverse AVS in hypercholesteremic rabbit models. We aim to determine whether ApoA-IM treatment decreased leaflet inflammation and calcification associated with atherosclerosis in vivo, and to study in vitro the putative mechanism of action of the observed effects.

Methods: In vivo: AVS was induced in rabbits (n=20) by 9-months of 0.2% cholesterol diet. The presence of AVS was detected at the end of induction by ultrasound. Animals were then randomized to either ApoA-IM (two i.v. infusions 75 mg/kg 4-days apart) or placebo. Four days after the last dose, aortic valves were explanted and leaflets analyzed for RAM-11, MCP-1, and calcification by histopathology.

In vitro: Porcine aortic valve myofibroblasts (PAVMF) were cultured with oxidized-LDL (50 μg/ml) for 7 days. Effects of ApoA-IM pre-incubation on alkaline phosphatase (AP) expression and activity, a major player in the calcification process, were assessed.

Results: In vivo: ApoA-IM significantly reduced macrophages infiltration (RAM-11+) of valve leaflet tips vs. placebo (6.5±7.1% vs. 17.5±9.5%; $p<0.05$). Percentage of the total leaflet MCP-1 positive was also reduced in ApoA-IM-treated animals (6.1±4.1% vs. 11.3±6.3%; $p<0.05$). Calcium deposits were observed in 88% (7/8) of untreated rabbits and in only 25% (3/12) of ApoA-IM-treated rabbits ($p<0.05$).

In vitro: ox-LDL significantly increased AP activity in PAVMF vs control (15.4±1.5 vs 12.3±2.3ng/106 cells; $p<0.001$). Pre-incubation with ApoA-IM (140μg/mL) completely prevented ox-LDL-induced changes in AP activity (11.5±0.7 ng/106 cells; $p<0.001$). Similar effects were seen on AP gene expression.

Conclusions: ApoA-IM significantly reduces hypercholesterolemia-related aortic valve inflammation and calcification in vivo and decreases AP expression and activity in vitro. Our data suggest that HDL-raising intervention may be effective agents not only for atherosclerosis but also for AVS treatment.